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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,912	01/11/2002	Noriyuki Kasahara	06666-125001 / USC2862	7224

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SCOTT C. HARRIS
Fish & Richardson P.C.
Suite 500
4350 La Jolla Village Drive
San Diego, CA 92122

EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/043,912	Applicant(s) KASAHARA ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-34 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 41-46, 49-51, 56, 58-61 and 63-82 of copending Application No. 10/045,178. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim gene therapy methods for treating any cell proliferative disorder (reading on any cancer) in any mammal comprising contacting the subject with a therapeutically effective amount of the recited recombinant oncoretroviral based retroviral vectors. The recited vectors can comprise chimeric targeting envelopes and/or tissue specific promoters for targeting the vectors to specific target cells or limiting transcription of the heterologous gene to cancer cells.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. The gene therapy art is extremely unpredictable. The unpredictability is manifested in the poor and unpredictable targeting of the gene therapy vectors to target cells, the transient and unpredictable expression of the transgenes in target cells, the unsuitability of many animal models of human cancers, etc. (For reviews of the unpredictability of the gene therapy art, see Anderson, Nature, 1998, Vol. 392, pp. 25-30; Kmiec, American Scientist, 1999, Vol. 87, pp. 240-247; Mountain, TIBTECH, 2000, Vol. 18, pp. 119-128; Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144, etc.). With regard to use of retroviral vectors to treat cancers, Gomez-Navarro et al. (European Journal of Cancer, 1999, Vol. 35, No. 6, pp. 867-885) notes

that "Lack of stability *in vivo* has confined the use of retroviruses to the *ex vivo* modification of target cells." (p. 876). Gomez-Navarro et al. further note that gene therapy strategies involving mutation compensation, molecular chemotherapy, genetic immunopotentation and viral-mediated oncolysis all suffer from serious shortcomings which have prevented them from being clinically successful. These shortcomings include poor levels of delivery of transgenes to target cells. Gomez-Navarro et al. note that: "Current vectors are far from achieving *in vivo* the requisite high levels of tumour cell modification." (p. 871). Additional shortcomings include those associated with molecular chemotherapy (i.e. enzyme/pro-drug strategies). Gomez-Navarro et al. note that the strategy of molecular chemotherapy has been limited to *in situ* schemes whereby the vectors are delivered directly to the tumor or to an anatomic compartment containing the tumor, but that:

"...transduction efficiencies of presently available vectors have been shown to be inadequate. Even in the context of closed compartment delivery, it has not been possible to modify a sufficient number of tumour cells to achieve a clinically relevant tumoral response..." (p. 873)

and that the levels of vector needed to transduce the majority of tumor cells are associated with limiting toxicity and therefore,

"...the small therapeutic index of currently available vectors in the context of *in situ* administration is a critical limiting factor for the purpose of gene therapy of cancer. Furthermore, and most importantly, a well-known limitation of conventional chemotherapy is also to be expected with the use of molecular chemotherapy, i.e. the appearance of drug-resistant tumour subpopulations (Table 1). In conclusion, vector limitations and well-known barriers to classical cytotoxic manoeuvres impede the full exploitation of the promise of a more selective eradication of carcinoma cells via the expression of toxin or protective genes." (p. 873).

Applicants also recite therapeutic use of retroviral vectors comprising targeting envelopes to deliver the vectors to target cells and transcriptional targeting comprising use of tissue specific promoters. However, Gomez-Navarro et al. notes that: "...modification of retroviral tropism has proven problematic, with few reports of modified envelope proteins which retain these two functions of binding and fusion..." (p. 878). Additionally, Paillard (Human Gene Therapy, 1998, Vol. 9, pp. 767-770) notes the numerous problems associated with attempting to redirect tropisms of retroviral vectors through use of chimeric envelopes expressed on the surface of said vectors. The chimeric envelopes are often not correctly folded, they may not be incorporated correctly on the viral surface, they may be able to bind to the target but not fuse with the cell membrane, etc. With regard to transcriptional targeting, Gomez-Navarro et al. notes that some regulatory elements lose their specificity in the context of some viral vectors and that the regulatory sequences are often so large as to preclude their use in smaller capacity viral vectors. Furthermore, with regard to promoters in retroviral vectors, attempted gene therapy using said retroviral vectors *ex vivo* (or *in vivo*) has been unsuccessful due to problems involving promoter silencing (possibly due to methylation of sequences in the vicinity of the promoter and/or incorporation of the transgene at the insertion site into condensed chromatin, See for example, Mountain, TIBTECH, 2000, Vol. 18, pp. 119-127, especially pp. 122-123) and unexpected shut down of transgene expression when cells transduced *ex vivo* are transplanted back into the host (See for example, Verma et al. Nature, 1997, Vol. 389, pp. 239-242, especially p. 240, cited by applicants).

Additionally, it is noted that all U.S. clinical studies involving use of recombinant retroviral vectors to deliver transgenes have been put on hold because of the possibility that the vectors may induce development of cancers in patients (Marshall, Science, 2003, Vol. 299, p. 320) as a result of random integration of the vectors into the cell genome. It is unclear how the skilled artisan would be able to use a retroviral based gene therapy method for treatment of cancer wherein administration of the vector itself may induce cancer development.

2) State of the art. The art with regard to successful clinical gene therapy treatment of cancers using recombinant retroviral vectors is poorly developed and is highly experimental in nature. Numerous significant hurdles to successful gene therapy need to be overcome before successful gene therapy for treatment of cancer can be enabled (See above discussion under "Unpredictability of the art").

3) Number of working examples. Applicants present no working examples of treatment of any cell proliferative disease.

4) Amount of guidance provided. Applicants provide data involving use of the recited retroviral vectors to transduce cells in vitro and in tumors in mouse xenograft model systems. Applicants show killing of cancer cells *in vitro* and infection and expression of transgenes *in vivo* in tumor cells in mouse xenograft models. However, there is no evidence of record to indicate that the results obtained by applicants would be predictive of the results the skilled artisan would expect to see in humans or other mammals suffering from cell proliferative disorders. It is noted that mouse xenograft models have

not been predictive of results which could be expected in humans (See Gura, Science, 1997, Vol. 278, pp. 1041-1042).

5) Scope of the invention. The scope of the invention is broad and reads on treatment of any cell proliferative disorder in any mammal.

6) Nature of the invention. The nature of the invention involves one of the most complex and unpredictable areas of medicine/molecular biology – gene therapy treatment of cancer.

7) Level of skill in the art. The level of skill in the art is very low. While the credentials of those of skill in the gene therapy art are impressive (M.D.s and Ph.D.s), their level of skill in actually practicing gene therapy for treatment of cancer is very low because they have not been successful in reducing gene therapy to practice.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Miscellaneous: Nucleotide sequences are present in Figures 1B and 9B. These sequences must be identified by SEQ ID NO: identifiers in the Brief Description of the Drawings section of the specification. Any response that does not include complete compliance with the Sequence Rules (37 CFR 1.821-1.825) will be considered to be non-responsive.

As part of the IDS filed 1/11/02, applicants have submitted a copy of a PTO-892 form from the parent application. A proper IDS should consist of citation of references on a PTO-1449 or PTO/SB/08A or 08B form. The references cited on the 892 form submitted by applicants have been considered by the examiner; however, applicants are encouraged to submit future citations of prior art on the appropriate forms.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
August 27, 2003

DAVID GUZO
PRIMARY EXAMINER